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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,724	12/08/2003	Antonius Arnoldus Christiaan Jacobs	I 1999.452 US C1	5481

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,724	JACOBS ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 06/22/06 has been acknowledged.
Claims 6-20 are pending and are examined in this office action.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/22/06 has been entered.

Double Patenting

Claims 6-11 and 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,682,745 for the same reasons of record as set forth in the office action mailed on 02/22/06,

Claims 6-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,120,775 (ref. of record), for the same reasons of record as set forth in the office action mailed on 02/22/06.

Response to Arguments

Regarding the double patenting issues above, the applicant requested the rejection be held in abeyance until allowable subject matter is identified, therefore the instant rejection has been maintained.

Claim Rejections - 35 USC § 112

Claims 6-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new mater). The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not tech the method as claimed especially in context of using the "live bacterial vaccine". The applicant fails to point out where in the specification there is support for the invention as claimed. The sole teaching in the specification is a throwaway line in which states "It is an object of the present invention to provide ways to diminish the problem of local reactions of live vaccines without further attenuating the live vaccines" (see spec page 1, lines 20-21). In addition the examples 1-3 (pages 7-9) fails to disclose that the pathogenic bacterial strains when injected submucosally provides immune protections against the pathogens thus meeting the definition of live bacterial vaccine. Therefore the invention as claimed is not supported by the specification as filed.

As MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." So claims 1 and 41-75 are apparently new matter. No pages or place in the specification was cited to support this amendment. A careful review by the examiner of the specification failed to identify any support for this new limitation. Since no basis has

been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Claims 6-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting a mammal against *Streptococcus equi* infection by submucosal administration of a live attenuated *Streptococcus equi* strain (TW980), does not reasonably provide enablement for a method for protecting a mammal against all bacterial infection by administering any live bacterial vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 02/22/06.

Nature of invention

The instant invention relates to administration of live bacterial vaccine(s).

Breadth of Claims and Guidance Provided in the Specification

The scope of the instant invention as claimed encompasses a method of administering a live bacterial vaccine (any bacteria) to a mammal by injecting the vaccine into submucosal layer of a mammal. The scope of invention as claimed further encompasses a method for reducing the amount of adverse reaction in a mammal at injection site of live bacterial vaccine (any bacteria) by administering the vaccine submucosally. The only disclosed utility of such a method is protection of animal against bacterial pathogens. The scope of invention as claimed broadly encompasses the use of any and all live bacteria. However, the instant specification only discloses the use of ***Streptococcus equi* attenuated strains** (TW 928 and TW928/sls), which are deletion mutant vaccine strains (spec. page 7, example-1). Besides TW 928 (*Streptococcus equi)* the instant specification fails to disclose any live attenuated vaccine obtained from any other bacterial strain. Especially, the specification fails to disclose a live vaccine obtained from *Actinobacillus equili, A. pleuropneumoniae, Actinomyces pyoyenes, Botdetella bronchiseptica, Brucella abortus, Clostridium perfringens, Corynebacterium bovis, C*

pseudotuberculosis, Erysipelotrix rhusioipathiae, Escherichia coli, Haemophilus parasuis, Leptospira canicola, L. hardjo, L icterohaemorrhagiae, L. poriona, Mycobacterium bovis, Mycoplasma bovis, M. hyopneumoniae, Noccatdia asteroides, Pasteurella haemolytica, P. multocida, Pseudomonas mallei, Rhodococcus equi, Salmonella cholerasuis, S. dublin, S. typimurium, Serpulina hyodysenteriae, Staphylococcus aureus, Streptococcus agalactiae, St. pneumoniae, St.suis, or St. uberis explicitly or implicitly as putatively claimed herein.

Response to arguments

The applicant arguments regarding enablement issue filed on 06/22/06 has been fully considered. The applicant argues that the invention as claimed is fully enabled to use any live bacterial vaccine. The applicant argues that the submucosal delivery of live bacterial vaccine generally result in reduced local response which is advantageous for less attenuated vaccines to be used. The applicant argues that applicant discovery is not limited to any single vaccine. The applicant argues that armed with the teachings of Applicants' specification, along with the knowledge already in the art, a skilled artisan would have sufficient knowledge to administer any given live vaccine in the manner claimed. The applicant argues that in general, a claim satisfies the enablement requirement if the specification enables a skilled artisan to make and use the claimed invention without "undue experimentation." The applicant argues that their claims satisfy the enablement requirement for reasons analogous to those in Wands. The applicant argues that i) the specification provides considerable direction and guidance for practicing the invention. ii) specification provides three working examples illustrating submucosal administration with four different live vaccines and two different host species. iii) The skill level in the art and nature of the technology are analogous to those in Wands. iv) The methods needed to practice the invention are well known in the art especially in context of making and using the live vaccines. The applicant provided a list of references that describe and uses live vaccines for various bacteria listed by the applicant. The applicant further provided list of various attenuated vaccines (see response pages 9-12) and concluded that law does not require applicants' specification describe every possible embodiment falling with in the claims.

However, applicant's arguments are found not persuasive because the scope of invention as claimed encompasses the use of any live bacterial vaccine instead of any live attenuated bacterial vaccine. The specification as filed fails to define what constitutes a live bacterial vaccine without any attenuation of the live vaccines. Thus the invention as claimed reads upon natural pathogenic strain of any bacteria especially as recited in claims 7, 11 12 and 20. A vaccine is an antigenic preparation used to produce active immunity to a disease, in order to prevent or ameliorate the effects of infection by any natural or "wild" strain of the organism (definition http://en.wikipedia.org/wiki/Vaccine). Accordingly the specification fails to disclose that submucosal (oral, nasal, rectal, vaginal etc) injection of any wild type bacterial strain as encompassed and recited in the instant claims would not cause infection but would provide protective immunity against that pathogen. For example the specification fails to disclose that submucosal injection of Clostridium. Esherichia, Salmonella or Streptococcus species as claimed would not result in bacterial infection leading to variety of pathogenic effects but lead to protective immunity against the pathogen.

State Of Art And Predictability

The state of the art at the time of filing teaches that the development of a bacterial vaccine is considered highly unpredictable because the safety and efficacy of the vaccine is dependent upon the way the bacterial antigens are presented to the host and the sate of the host immune response it self. Further more several safety concerns of the live bacterial vaccine strain have been raised. Before using pathogenic bacteria for vaccination purposes, its pathogenicity must be weakened via attenuation. Attenuation usually involves deletion of essential virulence factors or mutation of genes encoding metabolic enzymes whose function is essential for survival outside the laboratory. Inactivation of a metabolic gene has the advantage that the bacteria still express virulence determinants important to elicit a protective immune response. Appropriate stable auxotrophic strains are usually not able to replicate in the human body and can safely be used even in immune compromised individuals. Defined deletions of at least two metabolic essential genes are usually used and decrease the probability of reversion to virulence. In general the spread of live bacterial vaccines to

the environment is a concern. However, attenuated human pathogens are usually not adapted to live outside its host. (see page 6, Detmer et al, Microb Cell Fact. 23(5):1-12, 2006).

In addition the state of attenuated bacterial vaccine art teaches was such that a rational approach to design a live attenuated bacterial vaccine involves genetic modification of the bacterial pathogen to make the pathogen less virulent while maintaining the stability of protective antigen expression that provides immune protection. The attenuation should be an inherent property of the bacterial vaccine and not be dependent on fully functional host defenses and immune response capabilities. (Curtiss R. J. Clin. Invest. 110(8):1061-1066, 2002, ref. of record). In addition, the attenuation of a bacterium requires the modification of specific bacterial genes that render the bacterial strain non-virulent. For example, inactivation of PhoP/phoq regularoty system in S. typhi results in strains, which are suitably attenuated for use as vaccines (Tiball et al Vaccine 19:4175-4184, 20001, *ref of record*, see page 4177 sec 3.1). Furthermore, the development of live attenuated bacterial vaccine has not been always predictable. For example, development of a live attenuated *Shigella* vaccine that is sufficiently attenuated to be non-reactive yet adequately invasive to be highly immunogenic took 30 years in making, since it required substantial understanding of molecular genetic basis of virulence of *Shingella* (Curtiss page 1063, col.2). The specification fails to provide any guidance regarding how to make a live attenuated bacterium selected from the above-mentioned species (see claims 7, 11, 12 and 20). The specification fails to disclose what are the bacterial regulatory systems in these bacteria, mutation of which would result in the making of a live attenuated bacterial strain that would provide protect a mammal against any specific bacterial infection. The state of the art clearly teaches that understanding of regulatory pathways that affect bacterial virulence and protective antigens that provides long-term immune protection are consider germane to the development of a live attenuated bacterial vaccine.

Furthermore, use any live bacterial strain as vaccine purposes posses a serious health threat to host animal because the live bacteria can colonize at the mucosal epithelium (non-invasive strains) or penetrate the mucosa (invasive strains) to replicate

and elicits the pathogenic effects. For example live Streptococcus equi is considered highly pathogenic which is capable of infecting nasal mucosa and upper respiratory tract in horses (see Slater et al, AAEP Proceedings 46:10-20, 2000; Medina et al, Vaccine 19:1573-1580, 2001). At very best the instant specification discloses immune protections in horse using an attenuated *Streptococcus equi* strains (TW 928 and TW928/sls). However, the specification as filed fails to provide any evidence that the wild type live strain of Streptococcus equi when injected submucosaly does not elicits any pathogenic effects in any mammal.

The USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of skill.

The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case to practice the invention, as claimed one would require a live attenuated vaccine on hand. However the specification fails to provide any guidance regarding how make a live attenuated vaccine for all bacterial strains (other than *Streptococcus equi* attenuated strains TW928). At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be

expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

In addition, sub mucosal injection of any live bacterial strain (virulent) as vaccine is not considered routine in the art and without sufficient guidance to a specific bacterial strain and vaccination outcome base upon the immune protection the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The amount of undue experimentation required would include sub mucosal injection of any live bacterial strains (as claimed) and evaluation of vaccine efficacy in order to provide immune protection. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER